The natural history study of Becker muscular dystrophy

Published: 27-10-2014
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- To describe the variability in clinical characteristics and natural history of BMD.Secondary objective:- To assess the role of genetic, biochemical and radiographic markers on disease severity and variability of BMD.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Neuromuscular disorders
Study type	Observational invasive

Summary

ID

NL-OMON46870

Source
ToetsingOnline

Brief title
Natural history study of Becker muscular dystrophy

Condition

- Neuromuscular disorders

Synonym
Becker muscular dystrophy / BMD

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Neuromusculair onderzoeksbudget LUMC (Prof. dr. J.J.G.M. Verschuuren)

Intervention

Keyword: Natural history BMD

Outcome measures

Primary outcome

1.To describe variability in clinical characteristics and natural history of

BMD.

-To describe the variability in and pattern of skeletal muscle involvement

-To describe variability in functional impairment

-To describe the variability in cardiac involvement

-To describe whether pulmonary function is impaired

-To describe cognitive functioning in BMD

Secondary outcome

2. To establish genetic, biochemical and radiographic markers for disease

variability and severity.

-To determine if mutation type and location are correlated to disease severity.

-To assess the quantity and quality of dystrophin protein and proteins of the

DAG complex (dystroglycans, sarcoglycans, dystrobrevin, syntropin and nNOS)

correlated to disease severity.

-To compare dystrophin quantity between muscle biopsies of the anterior tibial

and quadriceps muscle.

-To compare dystrophin quantity and quality in new and old muscle biopsies

(only in patients who participated in our earlier study *Becker Muscular

Dystrophy: Analysis of diversity in disease severity*).

- To correlate proteins of the DAG complex with disease severity.

- To determine the inflammation markers in serum and on muscle MRI.

- To determine the role of exploratory biomarkers such as proteins (e.g. MMP-9

and fibronectin) and microRNAs (e.g. miR-1, miR-133)

Study description

Background summary

Becker muscular dystrophy (BMD), like Duchenne muscular dystrophy (DMD), is an X-linked inherited disorder (locus Xp21.2) caused by mutations in the dystrophin gene (DMD gene), coding for the protein Dystrophin.

Dystrophin protein plays an important role in stabilising the muscle fibre membrane. It is localized to the inner surface of the sarcolemma of muscle fibres where it interacts with other integral membrane proteins (dystroglycans, sarcoglycans, syntrohpin and dystrobrevin) of the dystrophin-associated glycoprotein complex (DAG complex) forming a bridge across the sarcolemma and thereby connecting the inner cytoskeleton to the extracellular matrix protecting the muscle fibres against contraction-induced damage. In the absence of dystrophin, as in DMD, or in the case of reduced amounts and/or abnormal functioning dystrophin, as in BMD, muscle fibres become susceptible to damage resulting in fibrosis and replacement of muscle fibres by fat.

Although BMD and DMD are caused by mutations in the same gene, BMD is characterized by a milder phenotype. A well accepted theory for this phenotypical difference lies in the reading frame theory. Mutations disrupting the reading frame (*out-of-frame*) prevent the production of dystrophin leading to a severe DMD phenotype. These patients develop muscle weakness in the early years of life and lose ambulation by their early teens and ,unless appropriate respiratory and cardiac treatment is initiated, affected individuals typically die before reaching their twenties. Mutations that do not disrupt the reading frame (*in-frame*) lead to the translation of an internally deleted but still partially functional dystrophin protein causing BMD phenotype. Clinical phenotype in these patients is highly variable with some patients able to experience a near normal life style and life span while others lose the ability to walk in their late teens or early twenties. Causes for this disease varibiability are not yet fully understood.

In this extensive follow-up study we want to further define the variability in clinical characteristics, disease severity and disease course in a large group of BMD patients and standardize muscle strength and functional tests for clinical follow-up. We want to explore factors involved in disease variability

such as dystrophin quantity/quality and identify potential genetic modifiers. Markers for disease variability, severity and prognosis will be explored in collaboration with the department for human genetics and the radiology department within the LUMC.

Study objective

- To describe the variability in clinical characteristics and natural history of BMD.
Secondary objective:
- To assess the role of genetic, biochemical and radiographic markers on disease severity and variability of BMD.

Study design

A single centre prospective natural history study: duration 4 years

Study burden and risks

During each visit several of the following examinations will be performed:
-Questionnaire: Every year
-Physical and neurological examination: Every year
-Muscle strength testing: Every year
-Functional assessment: Every year
-ECG, echocardiogram and holter registration: Year 1 and 3
-Pulmonary function test (handheld spirometer): Every year
-Blood and urine analysis**: Every year
-Muscle biopsy**: Year 1
-Muscle MR-imaging Only when also participatiing in the study "quantitative muscle MR-imaging of skeletal muscle in Duchenne and Becker muscular dystrophy: Year 1 and 2.

**This study is limited to two invasive procedures:
1. A venepuncture for blood withdrawal and one or two muscle biopsies.
2. A muscle biopsy which is performed under local anaesthesia. It does not require the patient to stay in the hospital after the procedure and does not impair normal daily activities afterwards. The complication risk is low and limited to a small possibility of development of a hematoma.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Diagnosis of BMD defined by:
-Male gender
-Progressive muscular weakness AND
-Elevated serum CPK-levels AND
-An in-frame mutation in the dystrophin gene AND/OR reduced amount of dystrophin protein in a muscle biopsy
2. BMD patients 18 years and older

Exclusion criteria

Patients will be excluded from muscle biopsies if they use oral anticoagulants.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	26-11-2017
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO

Date:	27-10-2014
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	01-05-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL50171.058.14